REMARKS

This Reply accompanies a Request for Continued Examination and addresses the issues of the final Office Action mailed 01/25/2007 (the "instant Action"). Claims 9-15, 23-29 and 48 are under examination all of which stand rejected.

In response to the instant Action, Applicants have canceled claims 4-6, 8-10 and 12-51 and added new claims 52-55. Applicants attest that the addition of new claims 52-55 neither introduces new matter nor requires a change of inventorship. Support for the new claims 52-55 can be found in claim 12 and other parts of the instant Application, as originally filed.

- Response to issues relating to the restriction requirement; request for rejoinder

In the instant Action, the Examiner made the restriction requirement final and maintained the objection to Claims 9, 10, 13-15 and 23-29 for allegedly reciting or encompassing non-elected inventions, while acknowledging that claims 11 and 12 were amended so that they recite only the elected subject matter.

In the instant Action (page 2, first paragraph), the Examiner cites "undue burden" in maintaining the restriction requirement to the single compound of claim 11. In response thereto, Applicants respectfully submit that the new claim 52 only recites three specific compounds – one of which is the same compound as that of claim 11 – and that these compounds are so closely related that a search and examination of these three compounds can be made without serious burden, even if, *arguendo*, they are directed to independent and distinct inventions. As such, pursuant to MPEP §803.03,[1] it is respectfully submitted that "the examiner must examine all the members of the Markush group in the claim on the merits." Specifically, all three compounds of claim 52 are human PTH analogues which selectively bind to the PTH2 receptor. Furthermore, all three compounds of claim 52 are substituted at the N-terminal putative helical domain with cyclohexylalanine, Cha. In support of this contention, Applicants hereby submit a Declaration by Dr. Michael Chorev under 37 C.F.R. §1.132 (the "Chorev Declaration") to the effect that the

[1] MPEP §803.02 provides "If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they may be directed to independent and distinct inventions."

three compounds of claim 52 selectively bind to the PTH2 receptor and are shown to significantly stimulate the cytosolic calcium secondary messenger pathway.

In addition, Applicants respectfully submit that claims directed to the methods of treatment (53-55) and the PTH2 receptor ligands listed in claims 11 and 52 are candidates for rejoinder upon the allowance of the product claims of claims 11 and 52. The method claims as set forth in claims 53-55 cannot be practiced with a materially different product nor can the novel PTH2 ligands be used in materially different process. Applicants respectfully request the reconsideration and withdrawal of the restriction imposed upon the instant Application and the allowance of all pending claims.

- Response to issues presented under 35 U.S.C. §112, first paragraph – written description

Claims 9, 10, 13-15 and 23-29 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Without conceding the correctness of this rejection and in an effort to solely overcome this rejection, Applicants have canceled claims 9, 10, 13-15 and 23-29. As mentioned in the instant Action, this rejection no longer applies to Claim 11 which has been amended.

Accordingly, Applicants respectfully request the reconsideration and withdrawal of claims 9, 10, 13-15 and 23-29 under 35 U.S.C. §112, first paragraph – written description.

- Response to issues presented under double patenting over claims 1-23 of U.S.P.N. 5,723,577

Claims 9-15 and 23-29 stand rejected under the judicially created doctrine of double patenting over claims 1-23 of U.S. Patent No. 5,723,577 (the "'577 Patent"). As noted above, Applicants have canceled claims 9-10, 12-15 and 23-29. As such, the instant double patenting rejection applies only with respect to claim 11, as presently amended, which recites the sole compound, [$Cha^{7,11}$, des-Met^{8}, Nle^{18}, Tyr^{34}]hPTH(1-34)NH_2 (SEQ ID NO:16), which selectively binds to the PTH2 receptor.

In the instant Action, the Examiner refers to Table I of the '577 Patent in support of her contention that

> The claimed analogues of Patent 5,723,577 are similar to the PTH analogues of the instant Application and therefore possess the same inherent characteristics as PTH2 binding affinity and efficacy ... . (page 8, 2nd paragraph).

However, the Kd and EC_{50} values of Table I of the '577 Patent are for the PTH analogues' ability to bind to the PTH/PTHrP (PTH1) receptor and their ability to stimulate adenylate cyclase activity. (*see* Col. 7-8 of the '577 Patent). It is important to note that, although binding to the PTH*1* receptor does result in some level of binding to the PTH*2* receptor, it does not necessarily result in ***selective*** binding to the PTH*2* receptor versus the PTH*1* receptor. It is not an inherent property, therefore, of compounds that bind to the PTH*1* receptor to ***selectively*** bind to the PTH*2* receptor. *Cf.* MPEP §2112, "The fact that a certain result or characteristic *may* occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. (emphasis original), citing *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). Also, "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted). Also, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species.).

Furthermore, the Examiner failed to establish that the claims of the '577 Patent suggest that the PTH/PTHrP analogues claimed therein bind selectively to the PTH2 receptors. *See, e.g.*, *Phillips Petroleum Co. v. U.S. Steel Corp.*, 673 F. Supp. 1278, 6 USPQ2d 1065, 1090 (D. Del. 1987), *aff'd*, 865 F.2d 1247, 9 USPQ2d 1461 (Fed. Cir. 1989) ("When considering the question of obvious variation, the patent disclosure may not be used as prior art. ... It is only that which is

related to and supported of the claim of the invention that may be used to determined the scope of the claim.").

Further in the instant Action, the Examiner states as follows:

> [T]here was no reduction to practice ... as far as measurement of PTH2 receptor binding. Nor were comparisons made between PTH2 receptor binding of the recited compounds and binding to other PTH receptors. It is not known if the claimed compounds are selective for the PTH2 receptor, or even how one would know from binding data what is meant in the claims by the word "selective." ... (paragraph bridging pp. 9-10).

In response to the Examiner's concerns, Applicants hereby submit the Chorev Declaration to the effect that the three compounds of claim 52 selectively bind to the PTH2 receptor and are shown to significantly stimulate the cytosolic calcium secondary messenger pathway. It is submitted that the experimental data on the three compounds of claim 52 in the Chorev Declaration are sufficient to provide experimental support for the claimed compounds, to the effect that the specific claimed compounds of the instant Application show unexpectedly superior results with respect to their ability to selectively bind to the PTH2 receptor and significantly stimulate the cytosolic calcium secondary messenger pathway, in such a manner heretofore unappreciated by the teaching of the '577 Patent.

As the Examiner acknowledges in the instant Action (page 9, last paragraph), the PTH2 receptor was not known at the time of filing of the '577 Patent. Thus the newly-discovered property of binding to the PTH2 receptor could not have been included in the '577 Patent. This is consistent with Applicants' argument that the instant Application is directed to Applicants' discovery of specific compounds – such as the single compound of claim 11 and the two additional compounds of claim 52 – that selectively bind to the PTH2 receptor. Nowhere in claims 1-23 of the '577 Patent is it suggested that the specific claimed compounds of the instant Application possesses the ability to selectively bind to the PTH2 receptor and to significantly stimulate the cytosolic calcium secondary messenger pathway. *See, e.g., Eli Lilly & Co. v. Barr Industries, Inc.*, 222 F.3d 973, 986, 55 USPQ2d 1609, 1918 (Fed. Cir. 2000) ("a species claim is not necessarily obvious in light of a prior art disclosure of a genus."); *In re Deuel*, 51 F.3d 1552, 1558-59, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995) ("A prior art disclosure of the amino acid sequence of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous

number of DNA sequences coding for the protein. No particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared."); *In re Baird*, 16 F.3d 380, 383, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("A disclosure of millions of compounds does not render obvious a claim to three compounds").

In the instant Action, the Examiner states that "Mere similarity of structure is sufficient to establish obviousness" (page 9, 1st full paragraph) without citing any authority. However, the Court of Appeals for the Federal Circuit has made it clear that that the claimed compound is a species of a genus disclosed in a prior art reference does not necessarily make the compound *prima facie* obvious. *See, e.g., In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). As such, absent a showing that the claims of the '577 Patent, aided by the disclosure of the '577 Patent to learn the meaning of the terms of the claims, would motivate a skilled artisan to envision the specific claimed compounds of the instant Application as selective ligands for the PTH2 receptor, it is respectfully submitted that the Examiner has failed to establish the *prima facie* case of obviousness. Even if, *arguendo*, the burden has shifted to the Applicants to prove nonobviousness, it is respectfully submitted that the experimental data on the three compounds of claim 52 in the Chorev Declaration are sufficient to provide experimental support for the claimed compounds, to the effect that the specific claimed compounds of the instant Application show unexpectedly superior results with respect to their ability to selectively bind to the PTH2 receptor and significantly stimulate the cytosolic calcium secondary messenger pathway, in such a manner heretofore unappreciated by the teaching of the '577 Patent.

Accordingly, reconsideration and withdrawal of the rejection of claim 11 under the judicially created doctrine of double patenting over claims 1-23 of the '577 Patent is respectfully requested. Furthermore, should the Commissioner determine that claim 11 is allowable, rejoinder of claims 52-55 is respectfully requested in view of the fact that the claims are limited to a reasonable number of specific compounds and that they share the common structural and functional characteristics as discussed hereinabove.

- Response to issues presented under double patenting over claims 1-16 of U.S.P.N. 5,717,062

Claims 9-15 and 23-29 stand rejected under the judicially created doctrine of double patenting over claims 1-16 of U.S. Patent No. 5,717,062 (the "'062 Patent"). As noted above, Applicants have canceled claims 9-10, 12-15 and 23-29. As such, the instant double patenting

rejection applies only with respect to claim 11, as presently amended, which recites the sole compound, [$Cha^{7,11}$, des-Met^{8}, Nle^{18}, Tyr^{34}]hPTH(1-34)NH_2 (SEQ ID NO:16), which selectively binds to the PTH2 receptor.

Applicants incorporate, as if stated in its entirety herein, the immediately preceding argument with respect to the obviousness-type double patenting rejection of the same claim over the '577 Patent. The Applicants note, however, that the Examiner states in the instant Action (page 10, second paragraph) that "the instant claims are so broad that there are no limitations whatsoever that would exclude [the claimed subject matter of the '062 Patent]." In response thereto, Applicants amended claim 11 to one specific compound and submitted the Chorev Declaration to provide experimental support for the claimed compounds of claims 11 and 52, to the effect that the specific claimed compounds of the instant Application show unexpectedly superior results with respect to their ability to selectively bind to the PTH2 receptor and significantly stimulate the cytosolic calcium secondary messenger pathway, in such a manner heretofore unappreciated by the teaching of the '062 Patent.

Accordingly, reconsideration and withdrawal of the rejection of claim 11 under the judicially created doctrine of double patenting over claims 1-16 of the '062 Patent is respectfully requested. Furthermore, should the Commissioner determine that claim 11 is allowable, rejoinder of claims 52-55 is respectfully requested in view of the fact that the claims are limited to a reasonable number of specific compounds and that they share the common structural and functional characteristics as discussed hereinabove.

- Response to issues presented under double patenting over claims 1-14 of U.S.P.N. 5,955,574

Claims 9-15 and 23-29 stand rejected under the judicially created doctrine of double patenting over claims 1-14 of U.S. Patent No. 5,955,574 (the "'574 Patent"). As noted above, Applicants have canceled claims 9-10, 12-15 and 23-29. As such, the instant double patenting rejection applies only with respect to claim 11, as presently amended, which recites the sole compound, [$Cha^{7,11}$, des-Met^{8}, Nle^{18}, Tyr^{34}]hPTH(1-34)NH_2 (SEQ ID NO:16), which selectively binds to the PTH2 receptor.

For the reasons stated hereinabove, Applicants respectfully request reconsideration and withdrawal of this rejection. Furthermore, should the Commissioner determine that claim 11 is allowable, rejoinder of claims 52-55 is respectfully requested in view of the fact that the claims

are limited to a reasonable number of specific compounds and that they share the common structural and functional characteristics as discussed hereinabove.

- Response to issues presented under 35 U.S.C. §102(b) over Gardella

Claims 9-15 and 23-29 stand rejected under 35 U.S.C. §102(b) as being anticipated by Gardella, et al. (1996, *J. Biol. Chem.*, 271(33):19888-19893). As noted above, Applicants have canceled claims 9-10, 12-15 and 23-29. As such, the instant §102(b) rejection applies only with respect to claim 11, as presently amended, which recites the sole compound, [$Cha^{7,11}$, des-Met^{8}, Nle^{18}, Tyr^{34}]hPTH(1-34)NH_2 (SEQ ID NO:16), which selectively binds to the PTH2 receptor, which compound is clearly not anticipated by Gardella.

Accordingly, absent a specific showing that Gardella is a novelty-destroying prior art reference with respect to the single PTH analogue compound of claim 11, as amended, Applicants respectfully request reconsideration and withdrawal of this rejection. Furthermore, should the Commissioner determine that claim 11 is allowable, rejoinder of claims 52-55 is respectfully requested in view of the fact that the claims are limited to a reasonable number of specific compounds and that they share the common structural and functional characteristics as discussed hereinabove.

- Response to issues presented under 35 U.S.C. §102(b) over Neugebauer and Willick

Claim 9 stands rejected under 35 U.S.C. §102(b) as being anticipated by Neugebauer and Willick (1993, *Peptides 1992*, C.H. Schneider and A.N. Eberle (eds), ESCOM Science Publishers). As noted above, Applicants have canceled claims 9-10, 12-15 and 23-29. As such, this rejection no longer applies to the instant Application. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection. Furthermore, should the Commissioner determine that claim 11 is allowable, rejoinder of claims 52-55 is respectfully requested in view of the fact that the claims are limited to a reasonable number of specific compounds and that they share the common structural and functional characteristics as discussed hereinabove.

- Response to issues presented under 35 U.S.C. §102(b) over U.S.P.N. 5,556,940

Claim 9 stands rejected under 35 U.S.C. §102(b) as being anticipated by Willick, et al., 1996 (U.S. Patent 5,556,940). As noted above, Applicants have canceled claims 9-10, 12-15 and 23-29. As such, this rejection no longer applies to the instant Application. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection. Furthermore, should the Commissioner determine that claim 11 is allowable, rejoinder of claims 52-55 is respectfully requested in view of the fact that the claims are limited to a reasonable number of specific compounds and that they share the common structural and functional characteristics as discussed hereinabove.

- Response to issues presented under 35 U.S.C. §102(e) over U.S.P.N. 5,717,062

Claims 9-15 and 23-29 stand rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent 5,717,062 (the "'062 Patent"). As noted above, Applicants have canceled claims 9-10, 12-15 and 23-29. As such, the instant §102(e) rejection applies only with respect to claim 11, as presently amended, which recites the sole compound, [$Cha^{7,11}$, des-Met^{8}, Nle^{18}, Tyr^{34}]hPTH(1-34)NH_2 (SEQ ID NO:16), which selectively binds to the PTH2 receptor, which compound is clearly not anticipated by the '062 Patent.

Accordingly, absent a specific showing that the '062 Patent is a novelty-destroying prior art reference with respect to the single PTH analogue compound of claim 11, as amended, Applicants respectfully request reconsideration and withdrawal of this rejection. Furthermore, should the Commissioner determine that claim 11 is allowable, rejoinder of claims 52-55 is respectfully requested in view of the fact that the claims are limited to a reasonable number of specific compounds and that they share the common structural and functional characteristics as discussed hereinabove.

- Response to issues presented under 35 U.S.C. §102(e) over U.S.P.N. 5,955,574

Claims 9-15 and 23-29 stand rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent 5,955,574 (the "'574 Patent"). As noted above, Applicants have canceled claims 9-10, 12-15 and 23-29. As such, the instant §102(e) rejection applies only with respect to claim 11,

as presently amended, which recites the sole compound, [Cha^{7,11}, des-Met^{8}, Nle^{18}, Tyr^{34}]hPTH(1-34)NH_2 (SEQ ID NO:16), which selectively binds to the PTH2 receptor, which compound is clearly not anticipated by the '574 Patent.

Accordingly, absent a specific showing that the '574 Patent is a novelty-destroying prior art reference with respect to the single PTH analogue compound of claim 11, as amended, Applicants respectfully request reconsideration and withdrawal of this rejection. Furthermore, should the Commissioner determine that claim 11 is allowable, rejoinder of claims 52-55 is respectfully requested in view of the fact that the claims are limited to a reasonable number of specific compounds and that they share the common structural and functional characteristics as discussed hereinabove.

CONCLUSION

Reconsideration of the instant Action, entry of the requested amendments and of the new claims as set forth herein, grant of request for rejoinder and allowance of the all pending and withdrawn claims are respectfully requested.

Prompt and favorable action is solicited.

Examiner Wegert is invited to telephone Applicants' attorney at (508) 478-0144 to facilitate prosecution of this application. With the exception of the fee for the aforementioned extension, Applicants are unaware of any additional fees due and owing with respect to this filing, however, if the Applicants' understanding is incorrect, the Commission is authorized to apply any charges and/or credits to Deposit Account No. 50-0590 referencing attorney docket number 073/US/PCT/US.

Respectfully submitted,

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